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Reverse epidemiology and hemodialysis blood pressure

To the Editor: Analyzing reverse causality in dialysis, Kalantar-Zadeh et al [1] address the blood pressure (BP) control issue and refer to Tassin unit experience in this issue of *Kidney International*.

In the studies cited by the authors, BP figures used as risk predictor are baseline values, most patients are hypertensive, antihypertensives are used in 65%, follow-up time is <5 years, and extracellular volume (ECV) is not mentioned. Conversely, in our own studies [2, 3], integrated BP values are used, BP is strictly normal, antihypertensives are seldom used, follow-up time is >10 years, and ECV control is a key point. Among 1235 Tassin patients, the lowest initial predialysis BP decile (1st dialysis month mean arterial pressure <90 mm Hg) mortality is significantly high (2 years odds ratio = 1.96, $P < 0.02$). Therefore, in Tassin as elsewhere, initially low BP does predict early mortality.

BP predictive value at dialysis initiation is poor: 90% of patients then are hypertensive, whatever their former hypertension exposure duration, and whether or not they become normotensive in dialysis. The effect of hypertension on target organs takes many years and very often we don't know how long a patient starting dialysis has been hypertensive. A recent report [4] clearly confirms the crucial predictive importance of hypertension duration before dialysis.

Reverse epidemiology has misleading relevance on dialysis management. The high early mortality universally associated with low baseline BP figures does not contradict the need to achieve normal BP in dialysis patients to reduce long-term cardiovascular mortality. Besides, the eventual noxious/beneficial role of antihypertensive medications in dialysis patients needs to be investigated.

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Reply from the Authors

Charra et al [1] indicate that in Tassin, a low, rather than elevated, blood pressure (BP) is associated with an almost 2-fold increase in mortality among maintenance hemodialysis (MHD) patients, despite long hours of dialysis treatment. This is consistent with our stated theory of reverse epidemiology. The study quoted by the authors indicating a positive association between hypertension and mortality in 184 Spanish MHD patients had a relatively small sample size [2]. Moreover, patients in this study were, on average, 10 years younger than MHD patients in the United States [3]. On the contrary, the epidemiologic studies indicating a strong association between low BP and mortality in MHD patients, which we [1] referred to, or which have been published elsewhere [4], examined many thousands of MHD patients with a low likelihood of selection bias.

It is not well established that treatment of hypertension by altering hemodialysis techniques or lengthening dialysis hours improves survival by reducing BP. Such treatments almost certainly change many other physiologic and metabolic conditions concurrently. Nonetheless, it is quite possible that if MHD patients lived longer, traditional risk factors such as hypertension might have the time necessary to exert their long-term deleterious effects. However, in MHD patients, malnutrition-inflammation complex syndrome (MICS) may independently cause high early mortality and reverse traditional risk factors [1]. Thus, it is possible, although not proven, that alleviation of MICS saves lives. Given the high mortality in MHD patients and failure of traditional risk factors to explain this, randomized clinical trials that test whether treatment of MICS reduces mortality are strongly indicated.

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Inadequacy of antiretroviral drugs dosage adjustment in HIV patients receiving dialysis

Letter to the Editor: Szczech et al [1] reported an interesting study in a recent issue of *Kidney International*. The authors reported the antiretroviral drugs dosing regimens they observed in their hemodialyzed patients. We further analyzed these dosing regimens and it appeared that dosage adjustement were most often inadequate for those patients with end-stage renal disease.

Table 1. Comparison of antiretroviral dosage reported in Szczech's study and available dosing recommendations for hemodialysis patients [2]

Drug	*N*	Dosage	Recommended dosage
Nucleoside reverse transcriptase inhibitors			
Abacavir[a]	3	300 to 600 mg/day	1200 mg/day
Didanosine	7	100 to 400 mg/day	50 to 100 mg/day
Lamivudine	36	25 to 300 mg/day	150 mg first dose then 25 to 50 mg/day
Stavudine	33	10 to 40 mg/day	15 to 20 mg/day
Zidovudine	11	100 mg 3 × a week to 600 mg/day	300 mg/day
Combivir®	8		
Lamivudine		150 to 450 mg/day	150 mg first dose then 25 to 50 mg/day
Zidovudine		300 to 900 mg/day	300 mg/day
Non-nucleoside reverse transcriptase inhibitors			
Efavirenz[a]	13	200 to 600 mg/day	600 mg/day
Nevirapine[a]	11	200 to 400 mg/day	200 to 400 mg/day
Protease inhibitors			
Indinavir[a]	6	1600 to 2400 mg/day	2400 mg/day
Nelfinavir[a]	21	500 to 2500 mg/day	2250 mg/day
Ritonavir[a]	5	200 to 1000 mg/day	1200 mg/day
Saquinavir[a]	2	800 to 3600 mg/day	1800 mg/day

N = Number of patients in Szczech's study.
Combivir®, 1 capsule contains 150 mg lamivudine and 300 mg zidovudine.
[a]Drug for which dosage adjustment is not necessary in hemodialyzed patients.

We read with great interest Szczech's article [1], in which they concluded that antiretroviral medications were not used at their optimal dose in the human immunodeficiency virus (HIV) hemodialysis patients they studied because data on these drugs' pharmacokinetics and dosage adjustment in patients with renal insufficiency are lacking. However, we would like to outline that most antiretroviral drugs' pharmacokinetics have been studied in patients with renal insufficiency.

Based on those publications and our personal data, we have recently published precise guidelines on antiretroviral drug dosage adjustment in hemodialysis patients [2]. Among the 11 antiretroviral drugs reported in Szczech's article, only 1 was administered at the correct dose (nevirapine). The other drugs that should have been prescribed at their usual dosage were either underdosed (abacavir, efavirenz, indinavir, nelfinavir, ritonavir, saquinavir) or overdosed (saquinavir). For the latter, the usual recommended dose for hemodialysis patients is 1800 mg/day [2]; the dosing range reported by Szczech is 800 to 3600 mg/day. Among the drugs that should have had their dose adjusted according to the patients' renal function, didanosine was clearly overdosed. Stavudine, lamivudine, and zidovudine administered alone were either under- or overdosed. Finally, the use of the lamivudine-zidovudine combination drug Combivir® led to a large overdose in all cases.

Consequently, although we agree that further pharmacokinetic, tolerance, and efficacy studies are mandatory for these patients, dose adjustment recommendations exist [2] and should already be routinely applied.

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Calcimetic AMG 073 at 50 and 100 mg per day

To the Editor: A comparison of the assessment against placebo of the calcimimetic AMG 073 at 50 [1] and